REMARKS

I. Preliminary remarks

Claims 89, 91-96, and 101-106 are pending. Claims 97-100 and 107-109 are withdrawn.

Claims 89 and 101 are amended herein. Support for these claim amendments can be found throughout the application as filed. See, for example, at pages 4, 11 and 15. Accordingly, no new matter has been added by the amendment to these claims.

The amendments made herein were made solely to expedite prosecution and not for reasons pertaining to patentability. Applicants reserve the right to pursue the subject matter of any claim (whether original, amended or canceled) in continuing applications.

II. The rejection of claim 101 under 35 U.S.C. § 101 is moot.

The Examiner rejected claim 101 as allegedly being directed to non-statutory subject matter. The rejection is moot in view of the amendment to claim 101 to recite an "isolated" polypeptide. Accordingly, the rejection should be withdrawn.

III. The rejection of claims 89, 91-96 and 101-106 under 35 U.S.C. § 112, first paragraph (written description), should be withdrawn.

The Examiner rejected claims 89, 91-96 and 101-106 under 35 U.S.C. § 112, first paragraph, as allegedly failing to be supported by the specification as filed. Applicants request reconsideration of the rejection in view of the amendments made herein and the following remarks.

The Examiner asserts that claim 89 allows for the polypeptide to have nearly no homology to the polypeptide of SEQ ID NO: 2 (sclerostin). This was not what Applicants intended. To improve clarity, claim 89 has been amended to recite that the polypeptide is at least 90% identical to the secreted *protein encoded by* a polynucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 5, 9, 11, 13 and 15. Thus there is a close structural relationship between SEQ ID NO: 2 and the polypeptide to which the claimed antibody binds.

The Examiner further asserts that claim 101 encompasses any polypeptide that is capable of binding to the secreted protein encoded by SEQ ID NO: 1, including ligands or receptors or other binding proteins, as long as the polypeptide is conjugated to an antibody fragment. In response, claim 101 has been amended to clarify that the polypeptide comprises an *antibody or antibody fragment that binds to sclerostin, i.e,* secreted protein encoded by SEQ ID NO: 1. Thus, the portion of the claimed polypeptide that confers sclerostin-binding properties is an antibody or antibody fragment.

The rejection of independent claims 89 and 101 under 35 U.S.C. §112, first paragraph, for assertedly lacking written description should be withdrawn because (1) Applicants have provided a representative number of species for the genus, and (2) Applicants have provided relevant identifying characteristics of the genus. There are two alternatives for satisfying the written description requirement for a genus: description of a representative number of species, or disclosure of relevant identifying characteristics of the genus. MPEP §2163 states that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above).

At Page 7 of the Action, the Examiner erroneously states:

> In this case, the only factor present in the claim [claim 89] is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved.

Claim 89 specifically recites that in addition to having 90% identity to the protein expressed by a polynucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 5, 9, 11, 13 and 15, the claimed polypeptide *also* retains a cysteine backbone comprising eight cysteines.

According to the written description guidelines for examination, analysis of a recited genus requires, first, that the Examiner determine if there is a representative number of species implicitly or explicitly disclosed. "What is a representative number of species depends on whether one of ordinary skill in the art would recognize the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed." [See page 3 of the Written Description Guidelines for Examination.] Applicants have provided seven different mammalian sequences, including three different naturally-occurring variants of the human sequence of "Beer" and the vervet, mouse, rat, and cow sequence of "Beer". The human and rat amino acid sequences are about 87% identical; the human and murine amino acid sequences are about 88% identical, and the human and vervet amino acid sequences are about 97% identical. Thus, Applicants have provided multiple species that exceed the breadth recited in claim 89 (90% identical). In view of the number of species mentioned above, Applicants submit that a "representative number" of species are described and the specification fully supports the genus recited in independent claim 89.

Moreover, Applicants have provided relevant structural features and other identifying characteristics. The specification describes the structure of seven different sequences. The specification provides comparisons between those sequences (falling within the genus) and other sequences, such as Dan, Gremlin and Cerberus, that fall outside the claimed genus. The specification discloses functional characteristics such as biological activity of altering bone density and bone mineral content. The specification also describes a correlation between structure and function. The claims recite structural features through percent identity language in addition to the cysteine backbone. For all of the reasons discussed above with respect to enablement, there is a correlation between the structural characteristics and the functional characteristics. Thus, the claims recite sufficient identifying characteristics to distinguish the claimed genus.

Applicants have not only provided a representative number of species but also sufficient identifying characteristics to define the genus. Moreover, because the specification provides a reference sequence (e.g., protein encoded by SEQ ID NOs: 1, 5, 7, 9, 11, 13, or 15) and describes a procedure to identify variants of said reference sequence (i.e., by percent

identity), one of skill in the art would realize from the specification that the inventors were in possession of the invention at the time of filing. For all of these reasons, there is adequate description of the claimed genus and the written description requirement should be withdrawn.

IV. The rejection of claims 89, 91-96 and 101-106 under 35 U.S.C. § 112, first paragraph (enablement), should be withdrawn.

In the action, the Examiner maintained the rejection of claims 89, 91-96 and 101-106 as allegedly failing to be supported by an enabling disclosure. The rejection is moot in view of the amendment to claims 89 and 91 made herein. As discussed above, the specification provides teaching that guides one of ordinary skill in the art where to make additions, substitutions or deletions, and how to screen the resulting variants for activity (e.g., the ability to decrease bone mineral content). For example, in the section describing how to make amino acid modifications to the protein, the specification states that the cysteine backbone of the protein (illustrated in Figure 1) should generally be conserved. See, e.g., page 21, line 7, page 26, line 29-page 27, line 1, and Figure 1. Moreover, the specification provides seven different sequences of native mammalian and variant human cDNA encoding a protein that decreases bone mineral content (SEQ ID NOS: 1, 5, 7, 9, 11, 13 and 15, see pages 81-84 of specification), from which one can determine which amino acids and regions are conserved among mammalian species. The Applicants previously provided a sample alignment of the coding regions of these sequences generated using CLUSTAL W (1.83) program, which indicated the conserved residues among these proteins. Earlier versions prior to the filing date (see, e.g., Higgins et al., "Using CLUSTAL for multiple sequence alignments," Methods Enzymol., 266, 383-402 (1996)) could easily have been used to generate a similar alignment, or visual inspection would have yielded the same information.

From this information, one of ordinary skill in the art could easily make knowledgeable choices regarding modifications; for example, conservative substitutions in the conserved regions are more likely to retain activity, while non-conserved regions are better able to tolerate non-conservative modifications. Similarly, substitutions in the cysteine backbone that affect folding are more likely to reduce activity. Moreover, the specification at page 63, lines 18-27 discloses various methods to determine bone mineral content or bone density.

Turning now to the rejection of claim 101, the Examiner does not appear to dispute enablement of antibodies or antigen binding fragments thereof directed to the polypeptide encoded by SEQ ID NO: 1. The concern appears to be enablement of any binding proteins that are ligands/receptors/interacting proteins for sclerostin. As noted above, claim 101 has been amended to clarify that the sclerostin-binding properties are conferred by comprising an *antibody or fragment thereof* that binds to the protein encoded by SEQ ID NO: 1. The specification discloses how to make and use antibodies that bind to the protein encoded by SEQ ID NO: 1. See pages 33-40 and 44-48 of the application as filed. The Examiner acknowledges at page 11 of the Action that antibody molecules are frequently linked to an auxiliary moiety. Fusion proteins, conjugate proteins and methods of making such proteins are disclosed throughout the application as filed. See, for example pages 5, 6 and 49 of the application as filed. Thus, claim 101 is fully enabled by the specification as filed.

In view of the foregoing, Applicants request that the rejection of claims 89, 91-96 and 101-106 as allegedly failing to be supported by an enabling disclosure be withdrawn.

V. The rejection of claims 89, 91-93 and 102 under 35 U.S.C. § 102(a) is moot.

The Examiner rejected claims 89, 91-96 and 102 under 35 U.S.C. § 102(a) as allegedly being anticipated by Valenzuela et al. (International Publication No. WO 98/49296). The rejection is moot in view of the amendment to claim 89 made herein. Valenzuela et al. does not disclose or suggest an antibody that specifically binds to a polypeptide at least 90% identical to the secreted protein encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 5, 9, 11, 13 and 15, as recited in claim 89. Accordingly, the rejection of claims 89, 91-96 and 102 under 35 U.S.C. § 102(a) is moot and should be withdrawn.

VI. The rejection of claims 101 and 103-106 under 35 U.S.C. § 102(e) is moot.

The Examiner rejected claims 101 and 103-106 under 35 U.S.C. § 102(e) as allegedly being anticipated by Rueger et al.. (U.S. Patent No. 6,949,505). The rejection is moot in view of the amendment to claim 101 made herein. Rueger et al. does not disclose or suggest an isolated polypeptide comprising an antibody (or antibody fragment thereof) that binds the

protein encoded by SEQ ID NO: 1, as recited in claim 101. Accordingly, the rejection of claims 101 and 103-106 under 35 U.S.C. § 102(e) is moot and should be withdrawn.

VII. Conclusion

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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